

In vivo assessment of the Combat Ready Clamp to control junctional hemorrhage in swine

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BACKGROUND: Junctional wounds and associated hemorrhage have become more common and more lethal in the current war. The Combat Ready Clamp (CRoC) has been developed and deployed for treating junctional hemorrhage on the battlefield. This study examined the efficacy of CRoC and its acute effects in an animal model.

METHODS: Anesthetized pigs ($n = 6$) were subjected to laparotomy, splenectomy, and abdominal closure. Next, coagulopathy was induced in animals by hemodilution and hypothermia. The left femoral artery was isolated, punctured (6-mm hole), and allowed to bleed for 15 seconds. The groin wound was packed with gauze, and a CRoC applied and tightened until hemorrhage stopped. It was kept in place for 1 hour (treatment period) and then released for another hour or less (control-period) if animal exsanguinated. Fluid resuscitation was administered, and vascular blood flow was examined by Doppler and CT scans. After death, local tissues were collected for histology.

RESULTS: CRoC generated 800 to 900 mm Hg pressure on the wounds, which stopped the hemorrhage and prevented rebleeding during the first hour in all animals. Blood loss was minimal (≤ 137 mL), and mean arterial pressure remained at or higher than the target level (65 mm Hg) during this period. Removal of the clamp promptly led to rebleeding and exsanguination of five of six pigs during the second hour despite fluid resuscitation. Blood loss, survival, shock indices, and other measures were significantly ($p < 0.01$) different between the two periods. Doppler tests and CT scans showed no blood flow in the proximal, distal, and collateral arteries of the clamped leg. Minor inflammation was seen on blood vessels (endothelium) and nerves.

CONCLUSION: CRoC functioned as an effective hemostatic adjunct for compression and control of groin hemorrhage. Although no acute histological damages were seen in compressed tissues, the short- and long-term effects of CRoC application (e.g., total ischemia) on limb function remain unknown and warrant investigation. (*J Trauma Acute Care Surg.* 2013;74: 1260–1265. Copyright © 2013 by Lippincott Williams & Wilkins)

KEY WORDS: Combat Ready Clamp; junctional bleeding; hemorrhage control; swine.

A recent autopsy analysis of 558 US military casualties who died of wounds after reaching a medical treatment facility from October 2001 to June 2009 by a panel of trauma experts showed that (a) 51.4% of causalities who died of wounds died of potentially survivable (PS) injuries, (b) hemorrhage was the main cause of death in 80% of these casualties, and (c) the PS injuries were focused on torso (48%), extremity (31%), and junctional (neck, axilla, and groin, 21%) body regions.¹ This report confirmed earlier autopsy analysis of a smaller group of in-hospital deaths ($n = 151$) that concluded that the delays in prehospital and in-hospital hemorrhage control were the primary contributors of potentially survivable deaths among casualties in a modern combat support hospital.²

The unsuccessful hemorrhage control of many casualties with PS extremity and junctional injuries (52%) emphasizes the need for better prehospital hemostatic therapies and devices.¹ The wide use of tourniquets (TQs) and hemostatic dressings in the current wars have reduced the incidence of exsanguination from isolated extremity injuries on the battlefield.^{3,4} However, neither method offers an effective means to control hemorrhage in casualties with junctional wounds. In

cases of high amputation, the wounds are larger and anatomically more complex with multiple vessels that are harder to compress with TQs than lower extremity wounds.⁵ The bleeding is also faster and unless controlled promptly it will result in rapid exsanguination.⁵ A capability gap for US military has been the treatment of compressible injuries where TQs cannot be applied and hemostatic dressing are ineffective.

In response to the challenge to control exsanguinating hemorrhage from junctional injuries, a research effort supported by the US Army Medical Research and Materiel Command was initiated to develop a specialized junctional bleeding TQs. In 2009, inspired by the abdominal TQ that was invented by Joseph Lister (1827–1912, surgeon), the pioneer of antisepsis,⁶ the Combat Ready Clamp (CRoC) with more flexibility and precision was developed (Combat Medical System, Fayetteville, NC). CRoC was designed to exert mechanical pressure directly over the wound or indirectly over the groin area to occlude underlying blood vessels and stop hemorrhage. The final design has a small cube (stored dimensions: height, 3.5 in; width, 11.5 in; diameter, 1.5 in) with an aluminum structure that weighs 1.6 lb. In 2010, it received the US Food and Drug Administration approval as a medical device for the control of difficult inguinal hemorrhage on the battlefield, and a limited number of devices were deployed for prehospital utility. CRoC is similar to an existing pneumatic compression device FemoStop® that is used in hospitals to assist hemostasis after diagnostic or therapeutic catheterization of femoral artery or vein. FemoStop has an inflatable pouch that allows accurate placement of precise amount of pressure (slightly

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above systolic pressure) on the catheter insertion site that not only prevents hemorrhage but also preserves distal blood flow. Although this device offers the convenience of hands-free hemorrhage control, it is also the source of some complications such as pseudoaneurysm and hematoma formation at the site of injury.^{7,8} Unlike CRoC, Femostop device has too large a cube to fit in medic's backpack and may not generate sufficient pressure to either directly control bleeding of large junctional wounds or compress proximal iliac vessels remotely to secure hemostasis in case of high leg amputation.

CRoC's hemostatic efficacy was demonstrated in a series of experiments at Wake Forest University School of Medicine's Center for Applied Learning using liquid-perfused human cadavers (unpublished data). The data showed that CRoC application on the groin area effectively occluded the vessels and stopped perfuse leakage from injury sites. These data were used in support of a Food and Drug Administration 510 (K) application to obtain marketing clearance. The efficacy and safety of CRoC had not been tested in live subjects until now.

The objective of this work was to conduct a proof-of-concept study to examine the effectiveness of CRoC to control arterial hemorrhage in a junctional wound model and to identify potential safety concerns related to CRoC application. For these purposes, we used our standard groin hemorrhage model in pigs⁹ with a preexisting coagulopathy.

METHODS

This study was approved by the Animal Care and Use Committee of the US Army Institute of Surgical Research. It was conducted in compliance with the Animal Welfare Act and implemented Animal Welfare Regulations. All animals received care and were used in strict compliance with the *Guide for the Care and Use of Laboratory Animals*.¹⁰

Yorkshire female crossbred pigs (36–42 kg) were purchased from Midwest Research Swine (Gibbon, MN). Upon arrival, the animals were housed and observed for 72 h to allow acclimation and exclude the possibility of preexisting disease by blood testing. Pigs were fasted for 12 to 18 h before surgery with free access to water. On the day of surgery, pigs were induced, intubated, and anesthetized by inhalation anesthesia (1–2% isoflurane) and mechanically ventilated as described previously.¹¹ Maintenance fluid (lactated Ringer's solution) was administered at 5 mL/kg/h intravenously. Body temperature was monitored with a rectal probe.

The common carotid artery, external jugular vein, and femoral artery were cannulated (via cutdowns) to monitor and record vital signs (systolic, diastolic, mean arterial pressure [MAP], and heart rate), collect blood samples, and infuse resuscitation fluid. After a midline laparotomy, splenectomy was performed, fluid replacement was administered (lactated Ringer's solution at 3× splenic weight), and the abdominal incision was closed with suturing. Coagulopathy was then induced in each animal by hemodilution (50% isovolemic blood exchange with Hextend) and moderate hypothermia (core temperature, ~34.5°C), as described previously.¹²

Next, an incision was made in the groin area, and the proximal segment of the femoral artery (4–5 cm) was dissected and freed from surrounding tissues. Before arterial injury and

hemorrhage, CRoC was partially assembled (base plate and vertical arm) and placed beneath the pig and adjacent to the groin area. The horizontal arm and the pressure screw with disc were also aligned with the artery to ensure direct pressure on the bleeding site when the CRoC was applied. Next, the injury (6-mm-diameter hole) was made in the femoral artery wall, and unrestricted bleeding was allowed for 15 seconds. The pretreatment bleeding time was shortened (as compared with 30 to 45 seconds in previous studies) to avoid a significant drop in blood pressure. The blood loss during this period was measured. The wound was then packed with several layers of 4 × 4-in surgical gauze, covered with a laparotomy sponge and compressed manually for 2 minutes. Afterward, the wound was observed for 2 minutes, and once rebleeding became evident (no possibility of hemostasis), the CRoC was fully assembled and its pressure disc was rapidly screwed down to exert enough pressure to stop the hemorrhage (Fig. 1). This pressure was measured after each experiment by placing a pneumatic cuff, connected to a digital barometer, beneath the pressurizing disk, and tightening the screw to the same level as was performed during the experiment.

The CRoC was left in place for 1 hour, and any blood loss during this period and during CRoC placement was collected and measured. Distal blood flow was checked with a Doppler every 15 minutes. At 1 hour, computed tomographic (CT) angiography was performed, and images of circulation through the vessels in the lower part of body were obtained. The clamped leg was then flexed and stretched a few times to mimic moving casualty and to determine the stability of the CRoC to maintain hemostasis. Next, the CRoC was removed, and the wound was observed for another hour or less if the animal exsanguinated. Blood loss during this period was also measured for comparison with the period that the clamp was applied. Limited fluid resuscitation (maximum of 3 L Hextend at 50 mL/min) was administered as needed to maintain MAP at or higher than 65 mm Hg. Arterial blood samples were collected at baseline, after hemodilution, at 60 min time point with clamp on and at the end of experiments for complete blood count, coagulation (PT, aPTT, and fibrinogen), and arterial blood gas analysis. Continuous data are expressed as median and

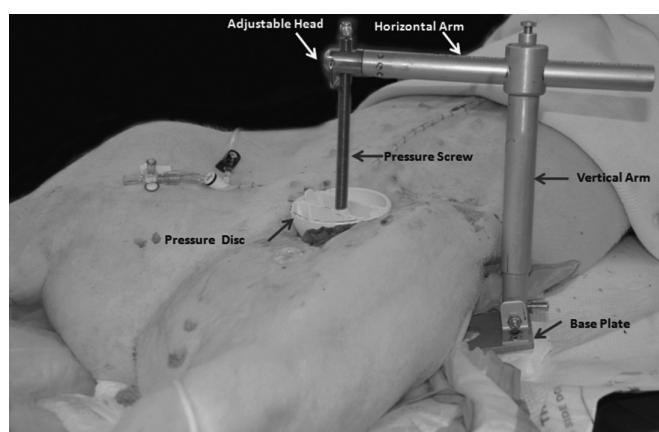


Figure 1. A photograph of the Combat Ready Clamp (CRoC) and its application to a pig groin wound.

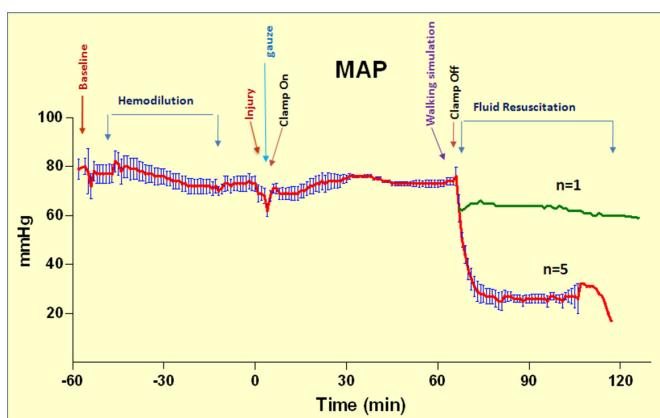


Figure 2. Mean arterial pressure (MAP) of pigs throughout the experimental procedures. The red line represents the average MAP of five animals that exsanguinated after removal of the CRoC, and the green line shows the pressure of a pig that survived.

interquartile range and analyzed by Wilcoxon matched pairs rank test. Binomial data were analyzed using Fisher's exact test.

RESULTS

The arterial injury caused profuse bleeding with an average blood loss of 126 ± 14.6 mL in 15 seconds before treatment. The application of the CRoC took on average 1.5 min (1.1–2.25 min range), during which CRoC was assembled fully and the pressure disk screwed down to generate enough pressure on the wound to stop hemorrhage. The produced pressure was 800 to 900 mm Hg or 15 to 17 psi, as measured after the experiments. The CRoC application stopped the hemorrhage and prevented rebleeding during the 1-hour observation in all animals ($n = 6$). The MAP was rapidly restored by placing the clamp and remained at or higher than 65 mm Hg with minimal fluid resuscitation requirement (Fig. 2).

Blood loss during the first hour of observation (clamp on) ranged from 52 to 188 mL, most of which occurred during the CRoC application period. The clamp remained in place during experiments, and moving simulation did not cause its slippage or rebleeding after the tests. Removal of the clamp at 1 h, however, promptly led to rebleeding in five of six experiments, and all animals were exsanguinated during the second hour of observation despite continuous fluid resuscitation. Significant rebleeding did not occur in one surviving animal after removal of the clamp, apparently due to the tight packing of the gauze into the wound by CRoC application. The overall hemostatic results are shown in Table 1. The laboratory blood test results measured at different phases of experiments are summarized in Table 2.

The CT scans and frequent Doppler tests of hind legs did not indicate any evidence of blood circulation in distal tissues when the clamp was applied on the wound. Moreover, the CT scans of arteries revealed the complete occlusion of external and internal iliac arteries above (proximal) the area applied with CRoC, with the complete absence of collateral blood flow in proximal and distal parts of limb. The images of a representative experiment before application (baseline) and 1 hour after application of the CRoC are shown in Figure 3. Histological examination of tissues in the wounds (skeletal muscle,

femoral artery, vein, and nerve) showed no significant damage associated with acute application of the CRoC. Only focal inflammatory cell (PMN) infiltration was seen on the endothelium layer of femoral veins and in perineural sheaths of femoral nerve (Fig. 4).

DISCUSSION

Improvised explosive devices (IEDs) have become synonymous with conflicts in Iraq and Afghanistan and have been the leading cause of death and injury among coalition forces.^{13–15} As with other fragmentation weapons, IEDs most commonly affect the extremities with upper and lower limbs affected equally.^{14,16} Data from the US Joint Theatre Trauma Registry show that after explosion, more than 70% of combat wounds are to the extremities, with head and neck injuries accounting for 20% to 25% of the wounds and torso injuries seen in less than 10% of combat casualties. The principles of treating IED injuries are the same as any other trauma with initial focus on control of hemorrhage and preservation of tissue perfusion and oxygenation. Tourniquets and topical hemostatic dressings have been instrumental in control of hemorrhage and saving lives when used for treating lower extremity injuries. However, these mechanisms are not effective or practical in stopping severe hemorrhage from junctional (groin, axilla and neck) or high amputation injuries.

The CRoC is the first hemorrhage control cleared by the US Food and Drug Administration in 2010 to treat junctional injuries on the battlefield. It is currently indicated only for control of difficult inguinal hemorrhage, but the company is conducting more experiments on human cadavers to demonstrate the efficacy of the device against other junctional hemorrhage and expand its indications to axilla and neck injuries. There is an anecdotal report of use of the CRoC in Afghanistan.¹⁷ It was placed on an Afghan man in his 30s with a left hindquarter amputation injury. According to the medic report, it took 90 seconds to apply the clamp, which promptly stopped the bleeding and allowed safe transportation of the casualty to

TABLE 1. Hemostatic Outcomes of CRoC Application and Release in a Pig Groin Hemorrhage Model

Values Median (25–75% IQR)	First 60 Min With CRoC (Treatment Period), n = 6	Second 60 Min Without CRoC (Control Period), n = 6	p
Hemostasis achieved/maintained	6/6	1/6	0.016
Time to hemostasis (min)	4.6 ± 4.3	Not measurable	—
Pretreatment blood loss (mL/kg)	3.2 ± 0.4	N/A	—
Posttreatment blood loss (mL/kg)	2.05 (1.4–3.1)	75.8 (38.8–82.1)	0.031
Hextend resuscitation (mL/kg)	0.0 (0–1.8)	40.9 (10.8–52.5)	0.031
Survival time (min)	60 (60–60)	37.5 (25.1–53.2)	0.062
Survival	6/6	1/6	0.016

The continuous data were analyzed using a Wilcoxon-matched pairs rank test, and binomial data were analyzed with Fisher's exact test.

TABLE 2. Blood Pressure and Hematological Data for Pigs at Different Time Points of Experiments

Values Median (25–75% IQR)	Baseline, n = 6	Posthemodilution, n = 6	First 60 Min With CRoC, n = 6	Second 60 Min without CRoC, n = 6
MAP (mm Hg)	78.0 (70.8–84.3)	70.0 (66–73.5)	69.5 (65.5–76.3)	17.0 (13.5–29.3)*
HGB (g/dL)	9.2 (8.9–10.6)	4.2 (4.0–4.8)	4.0 (3.9–4.8)	0.7 (0.5–2.3)*
HCT (%)	27.9 (26.8–31.9)	13 (12.1–14.7)	12.5 (11.8–14.4)	4.4 (2.9–10.7)*
PLT (1000/ μ L)	397 (362–439)	184 (168–203)	119 (154–198)	30.3 (6.6–138)*
PT (s)	11.2 (11–11.8)	12.4 (11.8–12.7)	12.0 (11.9–12.9)	20.1 (14.8–32.5)*
aPTT (s)	16.5 (15.9–16.9)	20.2 (19.3–21.4)	20.4 (18.8–22.3)	32.3 (24.1–50.9)*
Fibrinogen (mg/dL)	249 (243–345)	153 (139–281)	154 (113–256)	90.7 (75.2–93.7)*
pH	7.42 (7.41–7.43)	7.43 (7.41–7.45)	7.46 (7.42–7.48)	7.53 (7.46–7.55)
Lactate (mM)	1.7 (1.1–1.9)	2.4 (2.3–2.5)	1.7 (1.4–2.3)	10.3 (6.0–11.4)*
BE (mM)	4.5 (3.6–4.9)	5.2 (3.4–6.5)	7.2 (6.6–8.0)	-2.0 (-3.0–3.6)*
Temperature (°C)	37.5 (37.0–37.8)	34.7 (34.5–34.9)	34.7 (34.6–34.7)	34.1 (33.8–34.4)

*Data were significantly different ($p < 0.031$, Wilcoxon-matched pairs rank test) than the data measured at the first 60 min (with CRoC).

The second 60 min was the intended time point, but most measurements were performed at an earlier time before animal exsanguinations. HGB, hemoglobin; HCT, hematocrit; PLT, platelet; PT, prothrombin time; aPTT, activated partial thromboplastin time; BE, base excess.

an Afghan hospital. In our study, CRoC application also took 1 to 2 minutes, which may result in significant blood loss in the field. Given the cube and weight restrictions and requirements for flexibility and adjustability of the instrument, the current design of the CRoC (tested here) was finalized after testing many prototypes. To shorten CRoC application time, medics are carrying the instrument in a partially assembled and ready-to-use form (without the casing) in their backpack. We think that with more training and wider distribution of CRoC, medics will be able to complete the assembly and application of the CRoC in less than 1 minute.

The present study is the first experimental evidence that examined the efficacy of the device in a live subject with lethal hemorrhage. The data showed conclusively that the CRoC acts as an effective hemostatic adjunct capable of stopping high-pressure arterial bleeding in the groin area that otherwise was lethal when treated with standard dressing alone. The blood test results also confirmed the effectiveness of the CRoC in preventing hemorrhagic shock and in maintaining homeostasis of pigs during the experiments. The CRoC was stable and secured hemostasis during application time. Hind leg movement or transport of subjects in and out of operating room (to perform CT scanning) did not cause clamp slippage or rebleeding. CRoC was tested in otherwise healthy pigs with preexisting coagulopathy. It is recognized that in the field, CRoC is likely to be used shortly after the injury before any coagulopathy is developed. The reason for producing coagulopathy before testing the CRoC in our animal model was that despite a very severe arterial injury in some instances, packing the wound with regular gauze alone was sufficient to produce hemostasis.¹¹ In such cases, therefore, applying the CRoC would have been unnecessary, and its efficacy could not have been tested.

To achieve hemostasis in this study, the CRoC had to be applied at substantially higher pressure (10-fold) than the animals' systolic blood pressure. The high pressure generated may have been buffered by several layers of gauze that were placed on the wound. Therefore, the actual pressure transmitted to vessel wall and caused arterial closure may have been only

slightly higher than systolic pressure. The reason for packing the wound first with gauze and then applying the CRoC was that this sequence was the most likely manner that a groin wound would be treated in the field. In addition, the instrument is not sterile, and its direct contact with the wound should be avoided. The spherical round-shaped disc did not fit in the groin wound of the pigs and could not be pressed directly over the arterial injury site. CRoC's round disc that was used for groin wound compression is 3-in width (diameter) and 1.5-in height. This disc was used because it produced a more evenly distributed pressure over the wound and was less likely to crush underlying tissues. The instrument also has an alternative wedge disk (1-in thickness and 2.25-in length), which exerts pressure on a more focused area and maybe more appropriate for use on axilla wounds to occlude axillary vessels.

The CT scans show that pressure generated by the CRoC not only occluded the femoral artery but also occluded the proximal external and internal iliac arteries and effectively blocked all collateral circulation in the affected leg. The venous congestion seen on the treated leg was another indication that blood outflow was also blocked with the clamp as expected. The CRoC may be applied directly on a groin wound to control hemorrhage from a penetrating injury (as was performed in this study), or it may be placed above the injury site (e.g., on common iliac artery) in cases of high leg amputation or a large groin wound with multiple bleeding sites. Therefore, total limb ischemia is expected when the CRoC is used, and this ischemia may be more severe and widespread than that occurring after placing a regular TQ on the lower parts of the extremities. Previous experience has indicated that up to 2 hours of ischemia by TQ placement and the subsequent reperfusion injuries are well tolerated and cause no irreversible tissue damages or functional deficit in the limbs.¹⁸ In an experimental ischemia/reperfusion study, a 3-hour ligation of iliac artery with subsequent surgical repair and blood flow restoration was tolerated, and pigs recovered 84% of neuro-muscular function within 2 weeks.¹⁹ The safe duration that CRoC can be left on the wound needs to be determined given the excessive compression force and more severe and global

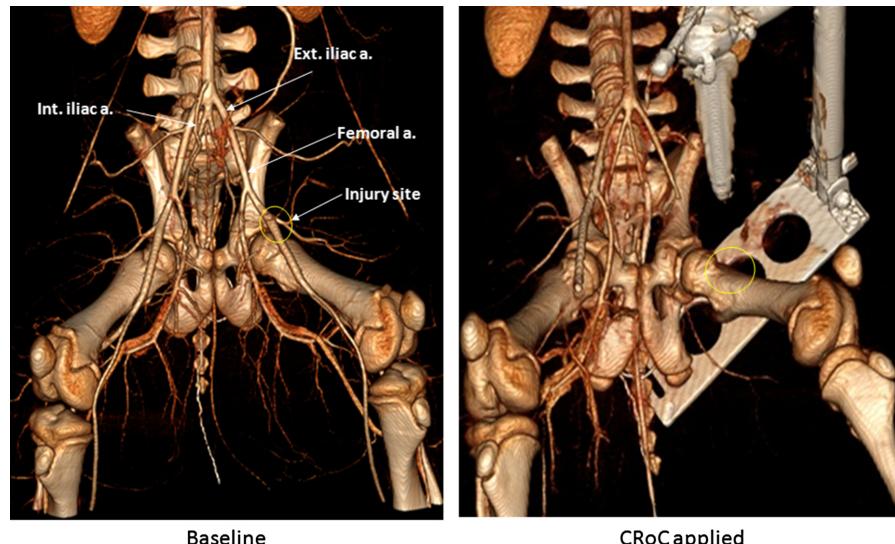


Figure 3. CT scans of arterial blood circulation before and after CRoC application. The yellow circles show the arterial injury site (baseline) and approximate spot where CRoC was applied. Note that the images of CRoC horizontal arm and pressure screw were edited out to reveal underlying structures.

ischemia that this device produces. In our follow-up study, we plan to apply the CRoC on the lower abdomen site to occlude the iliac vessels and see possible damaging effects on GI tract and urogenital tissue in survival studies.

Histological examination of tissues showed no significant acute damages on compressed blood vessels and nerves after a 1-hour CRoC application. The only abnormal findings were focal PMN infiltration of the venous endothelial cell layer and of the perineural sheath with unknown clinical significance. However, the reader should be reminded that the vessels and the nerves examined were not perfused with blood even after the release of the clamp. This was because the incoming blood entirely leaked out through the large arteriotomy. Therefore, the real effect of the ischemia and reperfusion injuries could not be seen in these unperfused tissues. The short- and the long-term functional recovery of the leg after CRoC

application also remains unknown. These safety issues warrant further investigation of the CRoC in a survival surgical model in which, after the CRoC application, the vascular injuries, and the wound are repaired surgically and the recovery of neuromuscular function is monitored over several weeks.

This study has several limitations that should be described. First, to test the efficacy of the CRoC, we used swine—which have a vastly different anatomy than humans—as the model. Unlike humans in whom the lower extremities comprise a large portion of the total body mass, the pigs' extremities account for smaller fraction and receive a smaller percentage of total blood flow than humans. Therefore, it may be easier to control an inguinal hemorrhage in pigs than that in humans. The effectiveness of the CRoC must still be confirmed in humans with junctional injuries. However, because clinical trials are not feasible, the only human data are the rare anecdotal reports that

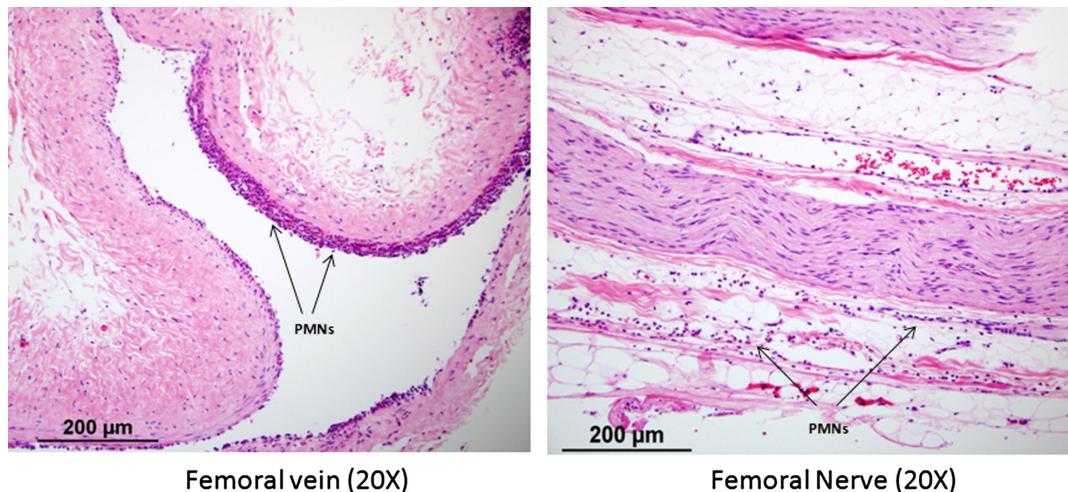


Figure 4. Micrographs of histological slides (hematoxylin and eosin stained) of uninjured tissues after a 1-hour application of a CRoC in groin wound. Note the PMN infiltration of perineural sheath and endothelium layer of the vein.

are gathered from the use of CRoC on the battlefield. Second, because this was a proof-of-concept study, the CRoC was tested under optimum conditions wherein it was preassembled and properly positioned before application on the wound. Hence, a time delay associated with these issues was obviated to observe the true potential of the CRoC. In combat situations, however, these issues are critical and may be much harder to resolve which may diminish the efficacy of the CRoC. Third, CRoC was tested in a small number of animals. This may seem to be another limitation, but the paired design of the study produced significantly different outcomes (main end points) that proved CRoC's efficacy, and therefore more animal testing could not be justified. Fourth, the CRoC was applied directly on a groin wound that was easy to locate and for which CRoC effects were readily observed. However, CRoC may be most beneficial for the control of hemorrhage in an inguinal amputation where no dressing or TQs can be applied. In such a case, the CRoC is applied above the injury site (on the lower abdomen) and tightened to occlude the iliac vessels, thereby stopping hemorrhage. Locating the right spot to apply the clamp that would occlude the iliac vessels will be harder than for a groin wound and will require training and practice on human volunteers or simulators. Application of CRoC on the lower abdomen site may cause significant damage to GI tract and urogenital tissues. Practicality and testing in human would be very important, and perhaps testing the CRoC in a catheterization laboratory may offer a useful human test environment.

In conclusion, the CRoC functions as an effective hemostatic adjunct for treating junctional (groin) wounds. Combined with ordinary gauze dressing, it consistently and securely (no slippage) stopped an arterial hemorrhage and prevented bleeding to death in a coagulopathic swine hemorrhage model. To achieve hemostasis, the CRoC generated high pressure over the wound that occluded major leg arteries and prevented all collateral circulation in the limb. Histological examination of affected tissues showed only focal inflammation of blood vessel lining and nerves with unknown clinical significance. The short- and long-term effects of CRoC's application and the consequences of total ischemia and reperfusion injuries of the treated limb remain unknown and warrant further investigation.

AUTHORSHIP

All authors were involved in the design of the study, methodology development, and preparation and editing of the article. Surgical procedures, treatments, data collection and analysis, and article preparation were performed by B.S.K. and I.B.T. Histological analysis was performed by M.A.H., our veterinarian pathologist. The study was guided by M.A.D. and L.H.B., Blackbourne who were also involved in the experimental design and preparation of this article.

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DISCLOSURE

The authors have no conflict of interest to report. This article is not an endorsement of the CRoC by the authors or the US Army but is simply a report of our observations with experimental use of the device. The

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